

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
20-873

CORRESPONDENCE



NDA 20-873

INFORMATION REQUEST LETTER

The Medicines Company
Attention: Sonja Loar, Pharm. D.
One Cambridge Center
Cambridge, Massachusetts

Dear Ms. Loar:

Please refer to your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax™ (bivalirudin) Injection.

Please commit, as a post-approval commitment, to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study.

We need your prompt written response to continue our evaluation of your NDA.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Lilia Talarico, M.D.
Division Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

/s/

Lilia Talarico

11/30/00 10:38:23 AM



NDA 20-873

DRAFT

The Medicines Company
Attention: Sonja Loar, Pharm. D.
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Ms. Loar:

Please refer to your new drug application (NDA) dated December 23, 1997, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax™ (bivalirudin) Injection.

We acknowledge receipt of your submissions dated April 6, May 12 and 17, July 14, October 9, November 9, and December 1, 2000. Your submission of July 14, 2000, constituted a complete response to our May 11, 2000, action letter.

This new drug application provides for the use of Angiomax™ (bivalirudin) Injection as an anticoagulant in conjunction with aspirin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA).

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon enclosed labeling text. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed labeling (text for the package insert) and submitted draft labeling (immediate container and carton labels submitted July 14, 2000). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 paper copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). For administrative purposes, this submission should be designated "FPL for approved NDA 20-873." Approval of this submission by FDA is not required before the labeling is used.

We remind you of your postmarketing commitment in your submission dated December 1, 2000. This commitment is listed below.

Commit to completing Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)" and submitting the full report for that study.

Final Report Submission: Within 54 months of the date of this letter.

Submit clinical protocols to your IND for this product. Submit nonclinical and chemistry, manufacturing, and controls protocols and all study final reports to this NDA. In addition, under 21 CFR 314.81(b)(2)(vii) and 314.81(b)(2)(viii), you should include a status summary of each commitment in your annual report to this NDA. The status summary should include expected summary completion and final report submission dates, any changes in plans since the last annual report, and, for clinical studies, number of patients entered into each study. All submissions, including supplements, relating to these postmarketing study commitments must be prominently labeled "Postmarketing Study Protocol", "Postmarketing Study Final Report", or "Postmarketing Study Correspondence."

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 FR 66632). We are waiving the pediatric study requirement for this action on this application.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-42
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

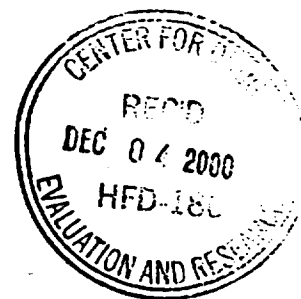
Sincerely,

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure



THE MEDICINES COMPANY



December 1, 2000

Lilia Talarico, M.D.
Director,
Division of Gastrointestinal & Coagulation Drug Products (HFD-180)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20-873
Angiomax™ (bivalirudin)
Submission #58

BL / GC
↓
(post-marketing commitment
and request for exclusivity)

Dear Dr. Talarico:

Please refer to your letter of November 30, in which you request us to make a post-approval commitment to complete Study TMC 98-10 entitled "Anticoagulant Therapy with Bivalirudin to Assist in the Performance of Percutaneous Coronary Intervention in Patients with Heparin-Induced Thrombocytopenia: An Open Label Study of Bivalirudin for Heparin-Induced Thrombocytopenia (HIT) or Heparin-Induced Thrombocytopenia and Thrombosis Syndrome (HITTS)". We hereby commit to completing enrollment and submitting the final report for this study to the Agency.

In addition, we would like to take this opportunity to claim 5 years of exclusivity for this compound under 21CFR 314.108(b)(2). To the best of our knowledge and belief, no other entity containing bivalirudin has been approved by the US FDA.

Enclosed is proposed labeling, incorporating the Divisional comments sent by the Agency on November 28. Changes from the July 14 labeling text are written in colored text; other text is black. A diskette containing this revised labeling is being forwarded directly to the project manager, Julieann DuBeau.

We look forward to discussing the tradename issue with you on Tuesday, Dec 5.

Thank you. If you have any questions, please contact Sonja Loar at (617) 225-9099 extension 584.

Regards,

Clive Meanwell, M.D., Ph.D.
Chief Executive Officer

ATTACHMENT

THE MEDICINES COMPANY

November 21, 2000

Julieann DuBeau, RN, MSN
Division of Gastrointestinal & Coagulation Drug Products (HFD-180)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

RE: Request for Teleconference

Dear Julie:

This letter serves to request a teleconference to discuss the proposed tradename (Angiomax™) for our compound, bivalirudin. Although OPDRA has no safety concerns regarding this name, apparently DDMAC has an objection. The Medicines Company respectfully appeals this objection. We understand that the basis of the DDMAC objection rests with the concept that the prefix "Angio" 'codes an indication'. In addition, the suffix "-max" is 'objectionable'.

Our appeal rests on two platforms: (1) we have already received a letter indicating acceptance of the name "Angiomax"; (2) the basis for the objection.

First, to address the prior approval of the name and the timing of this objection, a brief review of history is in order. The original NDA was submitted with the name Hirulog®, since the product is based on the structure activity relationships with the medicinal leech compound, hirudin. This is a name which has received much recognition in the scientific community. However, in April of 1998 the Agency opposed the use of the name Hirulog due to safety concerns regarding possible confusion with an existing marketed product: Humalog®. Therefore, in 1998 the company proposed a new trade name: Angiomax, and accepted the attendant loss of name-recognition.

In January 1999 the Division sent a letter to us indicating that the nomenclature committee was opposed to the suffix "-max" in the name. The Company appealed this position in February 1999. Subsequent to this appeal, the Company received a letter (June 21, 1999, attached) which stated, with regard to the name Angiomax:

One Cambridge C. eote: Cambridge, Massachusetts 02142 Tel: (617)225-9099 Fax: (617)225-2397

"We have completed our review of your proposed proprietary name and find it acceptable. However, please be advised that future approved indications may render this trademark 'misleading.'

The prefix "angio" is derived from the Greek term for vessel. We recognized the theoretical limitations of the "angio-" prefix for non-vascular indications, but took the Agency's word that it was at least acceptable for this initial approval and indication. Finally, on November 17, we were made aware that DDMAC objects to the name (especially the prefix, 'angio'). In sum, this objection comes after The Medicines Company has already changed the tradename once, mad almost a year and a half after the written acceptance by FDA of the name.

During this year and a half, based on our understanding that the name was acceptable, we have used the name Angiomax in clinical trials, in our investigator's brochure, and in launch-planning activities. A significant amount of resources have been expended supporting and utilizing this new name.

With regard to the basis of the objection, it is important to note that OPDRA does not have any safety concerns with regard to "sound alike" or "look alike" names. If this were the concern, we would change the name (as we already have once) to alleviate any safety concerns, because patient safety is our priority. However, the DDMAC concern is not about safety.

We have already communicated (Feb 24, 1999) that many names have "max" as either a prefix or suffix. In addition, there are many names which use "max" or "pro" and also contain a prefix or suffix which could be interpreted as alluding to the use of the drug (e.g. Maxair for bronchospasm, Flomax for BPH, Maxitussin as an antitussive, and Procrit for anemia). We have compiled a partial list of approved drug names which use "max" and/or which could be interpreted to allude to the use of the drug (attached).

Furthermore, given that this drug is intended for use by specialists in a highly specific setting (interventional cardiologists in the cath lab) we feel that the name alone will not inappropriately influence their patient management. If the product were to be marketed directly to consumers, there would be greater theoretical concern, although several of the products listed in the attachment are, in fact, marketed direct to consumers.

Upon review of the basis of DDMAC's concern, we believe that their position is not supported, and therefore (1) we appeal the objection and (2) propose that we discuss FDA's current position with regard to the tradename. Therefore, we request a teleconference with you and Drs. Talarico and Raczowski. If the teleconference is scheduled for Tuesday or Wednesday, we plan to have the following people on the call:

Sonja B. Loar, Sr. Dir. Reg Affairs

Phyllis Collins, Sr. Dir. Medical Affairs and Drug Safety

NDA 20-873

Page 5

Joan Barton, Dir. Reg Affairs
Clive Meanwell, CEO.

Please Call me to confirm the teleconference time at (617) 588-1584.

Regards,

Sonja Barton Loar, Pharm. D.
Sr. Director, Regulatory Affairs

Attachments

TRADENAME LIST:

Proprietary Name	Use/Indication
Flomax	BPH
Maxair Inhaler	bronchospasm
Maxitussin	anti-tussive
Procrit	treatment of anemia
Fosamax	osteoporosis
Maxaquin	antibiotic
Zithromax	anti-infective
Maxzide	anti-hypertensive
Maxitrol	ocular infection
Maxalt	migraine
Lotemax	anti-inflammatory
Topamax	seizures
Maxipime	antibiotic
Tamiflu	influenza
Neupogen	neutrophil regeneration/recover
Cardizem	cardiac indications (hypertension/angina)
Flonase	"management of nasal symptoms..."
Lipitor	lipid lowering agent
Unithroid	thyroid disorders
Visudyne	vision (macular degeneration)
Norvasc	hypertension/angina
Pletal	platelet inhibitor
Pulmicort	pulmonary/asthma
Rhinocort	allergic rhinitis
Singulair	asthma
Inomax	infant respiratory failure
Infasurf	surfactant for infants with RDS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

JUN 21 1998

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Dr. Lategan:

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We also refer to your submission dated February 24, 1999, in which you requested reconsideration of your proposed proprietary name Angiomax.

We have completed our review of your proposed proprietary name and find it acceptable.] However, please be advised that future approved indications may render this trademark misleading.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response; as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

Kati Johnson —
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

DuBeau

NDA 20-873

JUL 20 2000

The Medicines Company
Attention: Sonja Loar
One Cambridge Center
Cambridge, MA 02142

Dear Ms. Loar:

We acknowledge receipt on July 17, 2000, of your July 14, 2000, resubmission to your new drug application (NDA) for Angiomax™ (bivalirudin) Injection.

This resubmission contains additional clinical, biopharmaceutics, and chemistry, manufacturing, and controls (CMC) information submitted in response to our May 11, 2000, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is January 17, 2001.

If you have any questions, call me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-180/Reviewers and Team Leaders

DISTRICT OFFICE

JD/July 20, 2000 (drafted)

/S/7/20/00

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

(DDR: Update the user fee goal date based on the class of resubmission.)

NDA 20-873

MAY 11 2000

The Medicines Company
Attention: Phyllis Collins
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Ms. Collins:

Please refer to your new drug application (NDA) dated December 23, 1997, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Angiomax™ (bivalirudin) Injection.

We acknowledge receipt of your submissions dated October 15, 21, 25, 27, and 29, November 3 and 11, December 20 and 21, 1999, January 7, 19, and 28, February 14 and 24, March 15, 28, and 30, and April 10 and 25, 2000. Your submission of November 11, 1999, constituted a complete response to our October 28, 1999, action letter.

We also refer to your submission dated April 6, 2000. This submission has not been reviewed in the current review cycle. You may incorporate this submission by specific reference as part of your response to the deficiencies cited in this letter.

We have completed the review of this application, as amended, and it is approvable for the following indication: "Angiomax™ is indicated for use as an anticoagulant in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA)."

Before this application may be approved, you must adequately address the following deficiencies:

I. Biopharmaceutics

- A. Explain why the dose of bivalirudin is to be reduced by half for patients with moderate renal impairment as specified in Table 1 of your proposed package insert submitted November 11, 1999. Results from your ongoing study entitled "The influence of dose and kidney function on bivalirudin pharmacokinetics (PK) and pharmacodynamics (PD) in patients undergoing percutaneous coronary artery angioplasty (PTCA)" (Study No. TMC-98-09) demonstrate that there is only a 21% reduction in total clearance of bivalirudin in this group.
- B. Explain why the proposed 0.2 mg/kg/h dosing regimen is not adjusted for renal function.
- C. Determine the half-lives of bivalirudin in patients with normal renal function and in patients with mildly and moderately impaired renal function by modeling the observed

data obtained from Study No. TMC-98-09.

- D. Upon completion of Study No. TMC-98-09, provide PK/PD analyses of the activated clotting time (i.e., PK/PD modeling, etc. if appropriate) along with analyses for age and gender effects on PK and PD. When gender analyses have been completed, please assess PK/PD as a function of glomerular filtration rate (GFR). If recruitment of patients with severe renal disease is problematic, please contact the Division to discuss possible study modifications that might make patient enrollment easier (e.g., a reduced blood collection scheme).

II. Chemistry, Manufacturing, and Controls (CMC)

A. Drug Product

1. Include a maximum mixing time for the dissolution step of the bulk drug, with instructions on how to proceed if the drug does not dissolve in the stated time.
 2. Provide a copy of the revised manufacturing procedure for the drug product that incorporates the changes described in the November 11, 1999, submission.
 3. Specify the in-process control tests to be performed as part of the batch record that incorporates the latest appropriate versions of the methods. In addition, explain why the in-process control methods are stamped "Unofficial Not for Regulatory Submission."
 4. Submit revised specifications for the finished drug product that include current versions of the methods.
- _____
- _____
- _____
- _____
- _____
- _____
- _____
- _____

1 page(s) have been
removed because it
contains trade secret
and/or confidential
information that is not
disclosable.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Please note that sufficient data have been submitted to support a 12-month expiration date. However, an expiration date of eighteen months may be granted if an acceptable statistical analysis of data that includes the 9 month data point (5° C) is provided. Provide stability data in tabular format on diskette. Include the following parameters in the data-set: _____

Regarding your request of waiver for pediatric studies under 21 CFR 314.55, we have reviewed the information you have submitted on November 11, 1999, and agree that a waiver is justified for the pediatric population. Accordingly, a waiver for pediatric studies for this application is granted under 21 CFR 314.55.

Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

1. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
2. Retabulation of drop-outs with new drop-outs identified. Discuss, if appropriate.
3. Details of any significant changes or findings.

4. Summary of worldwide experience on the safety of this drug.
5. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
6. English translations of any approved foreign labeling not previously submitted.
7. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please send one copy to the Division of Gastrointestinal and Coagulation Drug Products and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, call Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely, /s/

5/11/00 FOR

Florence Houn, M.D., M.P.H., F.A.C.P.
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Marked-up Draft Labeling

NDA 20-873

MAR 2 2000

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Dr. Lategan:

Please refer to the meeting between representatives of your firm and FDA on February 4, 2000.

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions please call me at (301) 827-7310.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:

Archival NDA 20-873—

HFD-180/Div. Files—

HFD-180 J.DuBeau

JD March 2, 2000 (drafted)

TS/1/2/00

GENERAL CORRESPONDENCE (MINUTES SENT)

DuBeau

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, MA 02142

DEC - 2 1999

Dear Dr. Lategan:

We acknowledge receipt on November 12, 1999, of your November 11, 1999, resubmission to your new drug application (NDA) for Angiomax™ (bivalirudin) Injection.

This resubmission contains additional clinical, statistical, biopharmaceutics, and chemistry, manufacturing, and controls (CMC) information submitted in response to our October 28, 1999, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is May 12, 2000.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (601) 827-7310.

Sincerely,

/s/ 12-2-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-873
HFD-180/Div. Files
HFD-180/J.DuBeau
HFD-180/Shaw
HFD-180/Zhou
HFD-180/Robie-Suh
HFD-180/Talarico
HFD-870/Lee

HFD-870/Hunt

HED-715/Flyer

HFD-715/Rashid

DISTRICT OFFICE

JD/November 30, 1999 (drafted)

15/ 12/2/99

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)

(DDR: Update the user fee goal date based on the class of resubmission.)

Strongin

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
Vice President, Regulatory Affairs
One Cambridge Center
Cambridge, Massachusetts 02142

JUL 20 1999

Dear Dr. Lategan:

Please refer to your pending December 23, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We also refer to your submission dated March 3, 1999 which included: (1) analyses estimating the clinical effects of Hirulog™ and heparin compared to an imputed placebo in percutaneous transluminal coronary angioplasty (PTCA); (2) a summary of the clinical effects data previously submitted to the NDA from Phase II studies in PTCA and unstable angina; and (3) a review of evidence in support of the view that Hirulog™ is associated with less hemorrhage than heparin in PTCA for unstable angina with particular emphasis on potential confounding.

We are reviewing the Clinical and Statistical sections of your submission and have the following comments and information requests:

Clinical

For Study C92-304-1 and Study C92-304-2 separately:

1. Provide a listing, by treatment, of patients who, in the study report, were not judged to have had an MI, but who are now being classified as having had an MI.
2. Provide a tabulation of all patients who received no heparin prior to the study or after discontinuation of the study drug. Include in that tabulation: patient number, site, treatment, age, gender, yes/no for post-MI, yes/no for procedural failure (by original study definition and by the revised definition), yes/no for each component of procedural failure (including AVC and including MI by both the protocol specified definition and the revised definition), exact ACT values at baseline, exact ACT values during treatment, and days in hospital. For this subpopulation, provide a calculation of procedural failure by the protocol specified definition and for the new composite endpoint using the revised MI definition at seven days or end of hospitalization.
3. Under 21 CFR 314.50(d)(5)(vi)(b), we request that you update your NDA by submitting all safety information you now have regarding your new drug. Please provide updated information as listed below. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission. (2) other dosage forms, and (3) other dose levels, etc.

- A. Retabulation of all safety data including results of trials that were still ongoing at the time of NDA submission. The tabulation can take the same form as in your initial submission. Tables comparing adverse reactions at the time the NDA was submitted versus now will certainly facilitate review.
- B. Retabulation of dropouts with new dropouts identified. Discuss, if appropriate.
- C. Details of any significant changes or findings.
- D. Summary of worldwide experience on the safety of this drug.
- E. Case report forms for each patient who died during a clinical study or who did not complete a study because of an adverse event.
- F. English translations of any approved foreign labeling not previously submitted.
- G. Information suggesting a substantial difference in the rate of occurrence of common, but less serious, adverse events.

Statistical

For the comparisons between bivalirudin and heparin treatment groups:

1. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of the odds ratios, and the confidence intervals for the composite endpoint (death, revised MI, or revascularization) during the hospitalization period for Studies C92-304-1, C92-304-2 and the combination of Studies C92-304-1 and C92-304-2.

Provide this same information for the composite endpoint that contains AVC.

2. Provide an estimate of the difference in proportions, Fisher's exact test, odds ratios, standard errors of the difference in proportions, standard errors of the odds ratios, and the confidence intervals for the composite endpoint (death, original MI, revascularization or AVC) during the 7-day or hospitalization period for Studies C92-304-1, C92-304-2 and the combination of Studies C92-304-1 and C-92-304-2.

Provide this same information for the composite endpoint using the revised definition of MI rather than the original definition.

3. Provide a data diskette with data for: (1) revised MI; (2) procedural failures (death, revised MI, revascularization or AVC); and (3) three-component procedural failures (death, revised MI or revascularization).

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

JS 7/20/99

Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

NDA 20-873

Page 4

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-180/B.Strongin

HFD-180/K.Robie-Suh

HFD-720/MRashid

DISTRICT OFFICE

Drafted by: BKS/July 13, 1999

Initialed by: KRS/July 14, 1999

PF/July 16, 1999

KJ/July 17, 1999

final: BKS/July 19, 1999

filename: BKS/July 19, 1999

191 7-19-99

INFORMATION REQUEST (IR)

DuBeau

NDA 20-873

JUN 21 1999

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

Dear Dr. Lategan:

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We also refer to your submission dated February 24, 1999, in which you requested reconsideration of your proposed proprietary name Angiomax.

We have completed our review of your proposed proprietary name and find it acceptable. However, please be advised that future approved indications may render this trademark misleading.

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

ISI 6/21/99
Kati Johnson
Supervisory Consumer Safety Officer
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-180/J.DuBeau

HFD-180/Shaw

HFD-180/Duffy

DISTRICT OFFICE

R/d Init: Johnson 6/16/99

JD/June 10, 1999 (drafted)

IS/ 6/18/99

ADVICE (AD)

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

APR 29 1999

Dear Dr. Lategan:

We acknowledge receipt on April 28, 1999, of your April 26, 1999, resubmission to your new drug application (NDA) for Hirulog® (bivalirudin) Injection.

This resubmission along with your submission dated April 22, 1999, contain additional medical, statistical, biopharmaceutics, microbiology, and chemistry, manufacturing, and controls (CMC) information submitted in response to our November 18, 1998, action letter.

We consider this a complete class 2 response to our action letter. Therefore, the user fee goal date is October 28, 1999.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 4-29-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-873

HFD-180 Div. Files

HFD-180 J. DuBeau

HFD-180 Duffy

HFD-870 Lee

HFD-715 Al-Osh

DISTRICT OFFICE

JD April 29, 1999 (drafted)

/S/ 4-29-99

CLASS 2 RESUBMISSION ACKNOWLEDGEMENT (AC)



THE MEDICINES COMPANY

February 24, 1999

Lilia Talarico, M.D.
Director, Division of Gastrointestinal & Coagulation Drug Products
(HFD-180)
Food and Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 20-873 - Hirulog® (bivalirudin)
General Correspondence
Amendment # 18

Dear Dr. Talarico:

Thank you for forwarding your letter of January 13th, 1999) the recommendation of the Nomenclature Committee regarding the use of Angiomax as a proprietary name for bivalirudin. The purpose of this letter is appeal that recommendation.

In the opinion of the Nomenclature Committee the suffix "max" is exaggerating and misleading. We have conducted a brief search for currently approved drugs with "max" as either a prefix or suffix. As you can see from the list below several such drugs exist, and presumably are marketed with the approval of the FDA.

Proprietary Name	Use/Indication
Fosamax	Osteoporosis
Zithromax	anti-infective
Flomax	benign prostatic hypertrophy
Maxitussin	anti-tussive
Maxzide	hypertension
Maxitrol	ocular infection
Maxair Inhaler	Bronchospasm
Maxalt	Migraine
Maxaquine	anti-infective
Maxipime	UTI/pneumonia

Furthermore given that this drug is intended for use in a highly specified (Cardiac Catheterization Laboratory) setting by highly specialized interventional cardiologists (who in our experience are very data driven) we feel that a suffix alone is unlikely to inappropriately influence their patient management.

The second element of the Committee's comment regarding additional indications is well taken. However, our current application is for use as an anticoagulant in patients undergoing PTCA and our plan is only to develop bivalirudin for vascular indications. Therefore the prefix "Angio" cannot be construed as misleading.

DUPLICATE

Given that our publication and awareness programs really require an identifiable name, we would appreciate it if you could ask the Committee for a prompt reconsideration of their decision.

If you have questions about this submission or require further information, please call me at (617) 225-9099.

Sincerely,

A handwritten signature in cursive script, appearing to read "Tom Lategan".

Tom Lategan, Ph.D
VP, Regulatory Affairs

CSO/DuBeau

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

JAN 13 1999

Dear Dr. Lategan:

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We have completed our review of your proposed proprietary name, Angiomax, and find the proposed name unacceptable because the suffix "max" is exaggerated and misleading. In addition, if a new indication unrelated to vasculature is found, the prefix "angio" would be misleading.

Please submit an alternate proposed proprietary name.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 1-11-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-873
HFD-180/Div. Files
HFD-180/CSO/J. DuBeau
HFD-180/Duffy
HFD-180/Shaw
HFD-180/Choudary
r/d Init: Johnson 1/8/99
r/d Init: Talarico 1/11/99
JD/January 5, 1999 (drafted)

/S/ 1/11/99

ADVICE (AD)

CSO/DuBeau

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

FEB - 9 1999

Dear Dr. Lategan:

Please refer to the meeting between representatives of your firm and FDA on January 15, 1999.

As requested, a copy of our minutes of that meeting is enclosed. Please notify us of any significant differences in understanding you may have regarding the meeting outcomes.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 827-7310.

Sincerely,

/S/ 2-8-99

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

cc:
Archival NDA 20-873
HFD-180/Div. Files
HFD-180/J.DuBeau
JD/February 8, 1999 (drafted)

/S/ 2/8/99

GENERAL CORRESPONDENCE (MINUTES SENT)

CSO/DuBeau

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142

JAN 13 1999

Dear Dr. Lategan:

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We have completed our review of your proposed proprietary name, Angiomax, and find the proposed name unacceptable because the suffix "max" is exaggerated and misleading. In addition, if a new indication unrelated to vasculature is found, the prefix "angio" would be misleading.

Please submit an alternate proposed proprietary name.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 1-11-99
Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-873
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-180/Duffy
HFD-180/Shaw
HFD-180/Choudary
r/d Init: Johnson 1/8/99
i/d Init: Talarico 1/11/99
JD/January 5, 1999 (drafted)

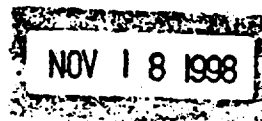
/S/ 1/11/99

ADVICE (AD)

CSD/DuFau

NDA 20-873

The Medicines Company
Attention: Tom Lategan, Ph.D.
One Cambridge Center
Cambridge, Massachusetts 02142



Dear Dr. Lategan:

Please refer to your new drug application (NDA) dated December 23, 1997, received December 23, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog™ (bivalirudin) Injection.

We acknowledge receipt of your submissions dated January 31, February 10 and 25, March 25, April 24, May 1 and 11, July 1 and 28, August 20, October 6 and 15, and November 3, 1998.

We also refer to your submission dated October 13 and 19, 1998, received on October 14 and 21, 1998, respectively. These submissions will be evaluated during the next review cycle. You may incorporate these submissions by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review and find the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b). The deficiencies may be summarized as follows:

Clinical:

Studies C92-304-1 and C92-304-2 were multi-center, double-blind, active controlled clinical trials with identical protocols. The primary objective of the studies was to demonstrate the superior efficacy and safety of Hirulog™ compared with heparin in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty (PTCA). The primary composite efficacy endpoint was "procedural failure" comprising death, myocardial infarction (MI), urgent revascularization, and abrupt vessel closure. The primary safety endpoints were the incidences of major and minor bleeding.

Superior efficacy of Hirulog™ compared with heparin was not demonstrated in either of the two studies, nor in an analysis which combined patient populations from the two studies. The efficacy results showed no statistically significant difference for the primary endpoint. Significantly lower rates of procedural failure were observed in the Hirulog-treated patients in the post-MI subgroup in Study C92-304-2. However, the number of patients in this subgroup analysis was small and the results were not replicated in Study C92-304-1.

In both studies, significantly fewer bleeding events, including major bleeding, occurred with the

use of Hirulog™ compared to heparin and fewer patients in the Hirulog™ groups discontinued treatment due to bleeding. However, this safety advantage may have resulted from increased bleeding risk in the heparin group because of the heparin regimen used for the studies.

Consider conducting an additional clinical trial, prospectively designed, to demonstrate superior efficacy and safety of Hirulog™, compared to heparin, in post-MI patients undergoing PTCA for the treatment of unstable angina. In addition, for the continued clinical development of Hirulog™ for any indication, you should assess the pharmacokinetic, pharmacodynamic, and safety of Hirulog™ in patients with renal impairment.

Chemistry, Manufacturing, and Controls (CMC):

[Redacted content]

(b4)

6 page(s) have been removed because it contains trade secret and/or confidential information that is not disclosable.

[REDACTED]

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Labeling comments will be forthcoming once the application is otherwise approvable.

The drug product may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely,

PS

11/17/18

Paula Botstein, M.D.
Acting Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-002/ORM

HFD-103/ADRA

HFD-95/DDMS

HFD-820/DNDC Division Director

DISTRICT OFFICE

HFD-180/DuBeau

HFD-180/Talarico

HFD-180/Robiesuh

HFD-715/Sankoh

HFD-715/Rashid

HFD-180/Choudary

HFD-180/Robison

HFD-870/J.Hunt

HFD-870/A.Selen

HFD-870/D.Lee

HFD-180/Duffy

HFD-180/Shaw

HFD-805/Cooney

HFD-805/Hughes

HFD-344/Malek

r/d Init: Botstein 11/16/98

r/d Init: Gibbs 11/16/98

r/d Init: Duffy 11/6/98, 11/16/98

r/d Init: Talarico 11/6/98, 11/16/98 (clinical section only)

r/d Init: Johnson 11/10/98

JD/November 5, 1998 (drafted)

NOT APPROVABLE (NA)

CSO/DuBeau

NDA 20-873

OCT 19 1998

The Medicines Company

Please refer to your new drug application (NDA) for Hirulog® (bivalirudin) Injection.

As you know, as part of the on-going process of reviewing your application, we have scheduled a meeting of the Cardiovascular and Renal Drugs Advisory Committee to consider issues concerning your application.

To assist your preparations for the upcoming meeting, we are enclosing a copy of the questions to be considered by the Advisory Committee.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure (1)

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-180/J.DuBeau

DISTRICT OFFICE

JD October 19, 1998 (drafted)

10/19/98

GENERAL CORRESPONDENCE

1501-5422
OCT - 9 1998

NDA 20-873

The Medicines Company

Please refer to your new drug application (NDA) for Hirulog® (bivalirudin) Injection.

As you know, as part of the on-going process of reviewing your application, we have scheduled a meeting of the Cardiovascular and Renal Drugs Advisory Committee to consider issues concerning your application.

To assist your preparations for the upcoming meeting, we are enclosing copies of the reviews pertinent to the issues to be discussed.

If you have any questions, contact me at (301) 443-0487.

Sincerely,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and Coagulation Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures: Medical and Statistical Reviews

cc:

Archival NDA 20-873

HFD-180/Div. Files

HFD-180/J. DuBeau

DISTRICT OFFICE

JD/October 8, 1998 (drafted)

GENERAL CORRESPONDENCE

The Medicines Company

JUN 15 1998

Please refer to your pending December 29, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog® (bivalirudin) Injection.

We also refer to your amendments dated January 31, 1998, in which you provided Biopharmaceutics data in ASCII file format on diskette; February 25 and March 25, 1998, in which you provided a partial response to the Agency's February 11, 1998, letter; and May 11, 1998, in which you provided a partial response to the Agency's February 11 and March 17, 1998, letters.

To continue our review of the Clinical Pharmacology and Biopharmaceutics section of your submission, we request the following:

A. Regarding the items requested in the February 11, 1998, Agency letter (see attached):

1. Please respond to the information requested in items D1, D2, D3, D8, and D10.
2. Item D4: Errors were noted in AUC and clearance calculations in your February 25, 1998, response to this item. Verify that AUC (0-tlast) values do not include an additional area calculated between the last detectable concentration and an assumed concentration of "zero" at the next sampling time. Regarding the clearance values provided, verify whether the doses listed in the C93-310 Study report (NDA volume 1.044, pages 180-186) or the clearances on page 4 of the February 25, 1998, amendment is correct. Also, provide a list of the dose and the AUC values used for calculation of the clearance parameters reported in this amendment.

In addition to Study C93-310, verify all of the AUC and clearance calculations in all of the bivalirudin studies for further consideration of these studies.

3. Item D5: Please address assay related issues identified during review of Study C93-310 as soon as possible. The assay method in the study report is inconsistent with the assay validation report in the NDA (Section 6) suggesting that the assay used for analysis of samples from this bioequivalence study was not validated. In addition, according to the study report (NDA volume 1.044, pages 15 and 16),

there were no quality control samples assayed during analysis of samples from this study, and the data from Subjects 7 and 13 suggest that there were fundamental analytical and/or procedural issues that need to be addressed. The analytical interference and/or sample handling issues should also be discussed in Items D1 and D2.

Address the detectable plasma concentrations of bivalirudin in the plasma sample of Subject 7 collected before the Hirulog dose. Explain how the bivalirudin concentrations in Subject 7's samples were verified. Unlike the bivalirudin concentrations in samples of other subjects, in samples from Subject 7 concentrations of bivalirudin were detectable up to 28 hours post dose (the last sample collected according to study protocol).

Plasma concentration-time data of Subject 13 suggest non-optimal analytical conditions, as detectable bivalirudin concentrations in plasma samples were observed only in samples collected at 1, 2, and 4 hours after the start of infusion. Address the analytical and procedural issues that could have resulted in these observations and what was done to further investigate the possible contributing factors.

Given the questionable and incomplete nature of Subject 13's data, calculation of pharmacokinetic parameters for this subject and inclusion of these parameters in the statistical analysis is considered to be an incorrect approach. It seems that this approach has resulted in the observed period and treatment interaction in AUC (0-28) or in the AUC (0-tlast) values.

Although statistical reanalyses of the recalculated parameter sets demonstrate that the two formulations are bioequivalent, given the assay related issues, validity of this bioequivalence study is questionable.

4. Item D6: Provide the manufacturing date for Lot 67X15W.
5. Item D7: Given the reported hepatic necrosis as stated in the pathologist's report of Study P8967-94-02 (NDA volume 1.002, pages 125 and 126 and March 25, 1998, amendment, page 52), the microsomal fractions obtained from these animals and used in Study P8967-94-06 are not considered to be suitable to assess lack of effect of bivalirudin on p450 isoenzymes. We object to the following statement in the NDA (Volume 1.002, page 51) "Hirulog exhibits low potential for adverse interactions with concomitant therapies. Hirulog does not affect hepatic p450 isoenzyme activity and therefore, should not affect p450 metabolism of concomitantly administered drugs that are cleared by the liver" and the fact that

Study P8967-94-06 was utilized to support this statement. In your March 25, 1998, amendment you state that "... the results [of Study P8967-94-06] suggest that exposure to Hirulog is 'unlikely to affect the hepatic P450-mediated metabolism of other concomitant therapies'." Please be advised that this claim cannot be supported with the currently available data. Consider revisiting this claim after the results of your proposed in-vitro study are available.

6. Item D9: Resolved.

B. Regarding the items requested in the March 17, 1998, Agency letter (see attached):

Please respond to all outstanding items.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 6-11-98
Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosures (2) Agency letters

cc:

Original NDA 20-873
HFD-180 Div. Files
HFD-180 CSO/J.DuBeau
HFD-870/Hunt
HFD-870 Selen
r'd Init: Talarico 6/11/98
r'd Init: Selen 6/9/98, 6/10/98
JD June 8, 1998 (drafted)

/S/ 6/11/98

INFORMATION REQUEST (IR)

DuBeau

NDA 20-873

The Medicines Company

APR - 1 1998

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog® (bivalirudin) Injection.

We have completed our review of your proposed proprietary name, Hirulog®, and find the proposed name unacceptable because Hirulog® sounds and looks similar to a currently marketed product, HUMALOG. In addition, there is a high potential for medication errors with these products since they are both parenteral products.

Please submit an alternate proposed proprietary name for Hirulog®.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/S/ 3-31-98

Lilia Talarico, M.D.

Director

Division of Gastrointestinal and Coagulation

Drug Products

Office of Drug Evaluation III

Center for Drug Evaluation and Research

cc:

Original NDA 20-873

HFD-180/Div. Files

HFD-180/CSO/J.DuBeau

HFD-180/Duffy

HFD-180/Shaw

HFD-180/Choudary

r/d Init: Johnson 3/31/98

r/d Init: Talarico 3/31/98

JD March 24, 1998 (drafted)

ADVICE (AD)

Dulan

NDA 20-873

The Medicines Company

MAR 17 1998

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog® (bivalirudin) Injection.

We also refer to your amendment submitted January 31, 1998, received February 4, 1998, in which you provided Biopharmaceutics data in ASCII file format on diskette.

Finally, we refer to your amendment submitted February 25, 1998, received February 27, 1998, in which you partially responded to the Agency's February 11, 1998, information request letter (see attached).

Regarding the Biopharmaceutics data submitted on diskette, which were individualized bivalirudin concentrations obtained for each study, please provide a new diskette containing ASCII files of pharmacokinetic/pharmacodynamic parameters for each one of these studies. These files should include, in addition to the parameters mentioned above, the appropriate formulation, sequence, period, and demographic information for each subject.

Regarding your responses to the Biopharmaceutics section of the Agency's February 11, 1998, letter, responses to items D4 and D9 are acceptable, however, further information is needed for items D5 and D7. Specifically, regarding item D5, the bioequivalence assessment for C93-310 needs to be repeated with the recalculated AUC values [AUC(0-tlast) and AUC(0-inf)]. In addition, please submit an ASCII file on a separate diskette for this study, of the bivalirudin parameters [Cmax, AUC values reported in the study report (AUC(0-28) and AUC(0-inf)) and the recalculated AUC values (AUC(0-tlast), and AUC(0-inf))] for each subject with their formulation, period, and sequence information.

Regarding item D7, you have indicated that the study report used for assessment of potential drug-drug interactions is Study Report P8967-94-06 in Volume 1.034, page 245. In Volume 1.034, on page 245, there are two Biogen study numbers (P8967-94-02 and P8967-94-06). It appears that the Study Number P8967-94-02 is for the 28-day toxicology study and the Study Number P8967-94-06 refers to the in vitro study conducted for assessment of potential drug-drug interactions with bivalirudin. It is possible that dosing information (preparation of dosing solution, verification of concentration of bivalirudin in dose solution, and stability in dosing vehicle) are included in the Study Report P8967-94-02, however, as this information is a

critical component of the Study P8967-94-06, it needs to be included in the Study Report. Please provide the dosing information (preparation of dosing solution, verification of concentration of bivalirudin in dose solution, and conditions of storage and stability of bivalirudin in the dosing vehicle) and copies of the supporting documentation. In addition, please verify whether the NOAEL dose in the rat, indicated to be 25 mg/kg/day, on page 123 of Volume 1.002 is accurate. Based on the information presented on Panel 3.5.6B, page 124 of Volume 1.002 (the status of rats after 28 days of intravenous infusion of bivalirudin), please address whether the conclusion of lack of potential drug-drug interactions with bivalirudin, derived from the results of Study P8967-94-02, is reliable.

Regarding item D8, in which you requested Agency feedback, please submit the proposed study protocol with detailed information on reasons for choosing to use "mitochondria" for assessment of potential drug-drug interactions instead of microsomal preparations as used in preclinical studies.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/s/ 3-17-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Attachment (1)

cc:

Original NDA 20-873
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-870/Hunt
HFD-870/Selen
r/d Init: Selen 3/16/98
r/d Init: Talarico 3/15/98

/s/ 3/17/98

NDA 20-873

Page 3

JD/March 16, 1998 (drafted)

INFORMATION REQUEST (IR)

Ames

NDA 20-873

The Medicines Company

JAN 15 1998

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Hirulog® (bivalirudin) Injection

Therapeutic Classification: Standard

Date of Application: December 23, 1997

Date of Receipt: December 23, 1997

Our Reference Number: 20-873

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on February 21, 1998, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact me at (301) 443-0487.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely yours,

Julieann DuBeau, RN, MSN
Regulatory Health Project Manager
Division of Gastrointestinal and
Coagulation Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

The Medicines Company

~~_____~~
~~_____~~
~~_____~~
~~_____~~

FEB | | 1998

Please refer to your pending December 23, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Hirulog® (bivalirudin) Injection.

To complete our review of your submission, we request that you submit the following:

A. Administrative

1. Revised, detailed index for the clinical technical section as well as Case Report Tabulations.
2. Proposed unannotated labeling on diskette in Word Perfect 6.1.

B. Clinical

1. Study protocols, amendments, and appendices on diskette.
2. Demographic and efficacy data for the two pivotal studies C92-304-1 and 92-304-2 in Paradox 5.0 for Windows data sets.

C. Chemistry/Manufacturing/Controls (CMC)

1. Statistical analysis of the stability data, including expiration date calculation; or, alternatively, a justification for not conducting the analysis.
2. Corrected stability report tables located in volume 1.003, pages 222 and 224.
3. Delineation of which stability reports are used to establish expiry and which are supportive.

D. Biopharmaceutics

1. Information for each validation study as follows: assay performance before and during sample analysis, preparation and performance of quality controls, raw data (including data utilized to construct the calibration curves), stability of

bivalirudin in samples, freeze-thaw stability, sample storage conditions, and assay validation. If one validation report supports multiple studies, please identify the validation report that supports each study.

2. Tabulated summary listing assay method, validated analytical range, the dates of assay validation, and sample analysis for each Hirulog® study.
3. Information on the methods and equipment used for aPTT measurements by study and the site where the measurements were made as well as how the equipment was calibrated.
4. AUC values calculated from time zero to the time of last detectable bivalirudin plasma concentration AUC (0-t) instead of AUC (0-28). Verify that clearance was calculated as the ratio of dose to AUC (0-∞). Please provide recalculated clearance values for study C93-310.
5. Your assessment of possible contributing factors of period effect and period and treatment interaction for study C93-310.
6. List of bridging studies to accommodate the major manufacturing and formulation changes with lot numbers of the formulations used, a description of the major changes, methods, dates of study conduct, report numbers, and their location in the NDA submission.
7. Clarification as to whether the reference made to an in vitro metabolism study in which rat hepatocytes were used for assessment of potential drug-drug interactions with P450 isozymes is based on the P8967-92-08 study report. If not, please provide the study report number and its location in the NDA submission.
8. In vitro assessment of potential drug-drug interactions for bivalirudin utilizing human hepatocytes by April 1, 1998.
9. Duration of infusion in Panel 3.6.3.B., volume 1.002, page 150.
10. Explanation of omission of recommended dose adjustment in patients with renal impairment in the proposed package insert.

E. Microbiology

Copy of CMC volumes 1.003-1.007.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Julieann DuBeau, Regulatory Health Project Manager, at (301) 443-0487.

Sincerely yours,

/s/ 2-11-98

Lilia Talarico, M.D.
Director
Division of Gastrointestinal and Coagulation
Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:

Original NDA 20-873
HFD-180/Div. Files
HFD-180/CSO/J.DuBeau
HFD-180/Talarico
HFD-180/Robie-Suh
HFD-180/Duffy
HFD-180/Shaw
HFD-870/Hunt
HFD-870/Selen
HFD-820/ONDC Division Director (only for CMC related issues)
r/d Init: Shaw 2/9/98
r/d Init: Selen 2/9/98
r/d Init: Robie-Suh 2/9/98
r/d Init: Talarico 2/10/98
JD, February 4, 1998 (drafted)

/s/ 2/11/98

GENERAL CORRESPONDENCE

cc:

Original NDA-20-873

HFD-180/Div. Files

HFD-180/CSO/J.DuBeau

HFD-180/Talarico

HFD-180/Robie-Suh

DISTRICT OFFICE

JD/January 14, 1998 (dra.

/S/ 1/15/98

ACKNOWLEDGEMENT (AC)